supported by claim 6 as originally filed, and is made to clarify that the phrase "the SCA2 coding portion set forth in" modifies both of the sequence identification numbers recited in the claim.

The subject matter of canceled claim 60 has been incorporated into claim 1.

The amendment to claim 61 is made to correct the dependency of the claim in view of canceled claim 60.

New claims 62, 63, and 64 are supported by, for example, originally filed claims 1 and 5.

Priority

The present application claims priority under 35 U.S.C. §U.S.C. 371 to PCT/US97/07725, filed May 8, 1997, U.S. Patent Application Serial No. 08/727,084 ('084), filed October 8, 1996, U.S. Provisional Application No. 60/022,207 ('207), filed July 19, 1996, and U.S. Provisional Application No. 60/017,388 ('388), filed May 8, 1996. Applicant respectfully disagrees with the assertions made at page 2 of the Action as they pertain to SEQ ID NOs: 4 and 5.

It was asserted that SEQ ID NOs:4 and 5 were first disclosed in the present application and the priority to the 371 application also does not disclose the instant SEQ ID NOs:4 and 5. This is not true. SEQ ID NOs:4 and 5 of the present application are identical to SEQ ID NOs:4 and 5, respectively, of PCT/US97/07725. Accordingly, claims 4-6 have the priority of the filing date of PCT/US97/07725, which is May 8, 1997.

The Examiner is requested to note that a portion of SEQ ID NO:4 and SEQ ID NO:5 have priority dates of October 8, 1996. The present application is a continuation in part of the '084 application, which was filed October 8, 1996. Nucleotides 38 - 1181, 1183 - 1247, and 1249 - 1259 of SEQ ID NO:4 of the present application were disclosed in the '084 application at SEQ ID NO:4 at the time of filing. Amino acids 1 - 377, 379 - 399, and 401 - 403 of SEQ ID NO:5 of the present application were disclosed in the '084 application at SEQ ID NO:5 at the time of filing.

Regarding the assertion that SEQ ID NOs:1-3 were first disclosed in the parent application 08/727,084, which was filed October 8, 1996, Applicant wishes to clarify that portions of SEQ ID NOs:1-3 have priority dates of May 8, 1996 and July 19, 1996.

SEQ ID NO:1

Figure 2 of the '388 provisional discloses nucleotides 193 to 509 of Figure 2 (SEQ ID NO:1) of the present application, with the exception of nucleotides 245, 272, 275, and 297-298, which are disclosed in Figure 2 of the '388 provisional as "N." The term "N" is well known to the art as referring to any one of the four nucleotides A, T, G, or C. Thus, nucleotides 193 to 509 of Figure 2 (SEQ ID NO:1) of the present application have a priority date of 8 May 1996.

Figure 2 of the '207 provisional discloses nucleotides 1-192 and 510-516 of Figure 2 (SEQ ID NO:1) of the present application. Thus, nucleotides 1-192 and 510-516 of Figure 2 (SEQ ID NO:1) of the present application have a priority date of 19 July 1996.

SEQ ID NO:2

Figures 6a and 6b of the '207 provisional disclose nucleotides 389-3286 and nucleotides 4019-4479 of Figures 6a and 6b (SEQ ID NO:2) of the present application. Thus, nucleotides 389-3286 and nucleotides 4019-4479 of Figures 6a and 6b (SEQ ID NO:2) of the present application have a priority date of 19 July 1996.

SEQ ID NO:3

Figures 6a and 6b of the '207 provisional disclose amino acids 77-1041 of Figures 6a and 6b (SEQ ID NO:3) of the present application. Thus, amino acids 77-1041 of Figures 6a and 6b (SEQ ID NO:3) of the present application have a priority date of 19 July 1996.

Rejections under 35 U.S.C. §112, first paragraph

Claims 1-3 were rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor had possession of the claimed invention at the time the application was filed. Specifically, it was asserted that the essential elements of the claims are drawn to isolated nucleic acids encoding **any** mammalian SCA2 polypeptide wherein the isolated nucleic acid is either DNA or cDNA (emphasis in original). This rejection, as it relates to the

pending claims, is respectfully traversed.

Claim 1 has been amended to recite an isolated mouse or human nucleic acid encoding an SCA2 polypeptide. Reconsideration and withdrawal of this rejection is respectfully requested.

Claim 4 was rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor had possession of the claimed invention at the time the application was filed. Claim 4 has been canceled, thereby rendering this rejection moot.

Rejections under 35 U.S.C. §112, second paragraph

Claim 5 and 6 were rejected under 35 U.S.C. §112, second paragraph. These rejections are respectfully traversed.

Claim 5 was rejected over the recitation "coding portion of nucleotides 1-516 of SEQ ID NO:1." Specifically, it was asserted that it was unclear whether the recitation was directed to nucleotides 1-516 of SEQ ID NO:1, or whether the recitation "coding portion" was also directed to nucleotides 163-4098 of SEQ ID NO:2, or also directed to nucleotides 50-3454 of SEQ ID NO:4. A person of ordinary skill would recognize that this recitation defines the metes and bounds of the claims. Even if this recitation caused the metes and bounds of the claims to not be readily recognizable to one of skill in the art, the meaning of the recitation is clear in view of the disclosure. The specification discloses that SEQ ID NO:1 is a genomic DNA, SEQ ID NO:2 is a cDNA, and SEQ ID NO:4 is a cDNA (page 49, line 28 through page 50, line 7). It is also disclosed that nucleotides 1-499 of the genomic DNA sequence of SEQ ID NO:1 corresponds to nucleotides 392-890 of the cDNA sequence of SEQ ID NO:2 (page 7, lines 22-24). A person of skill in the art would recognize that the recitation "coding portion" modifies SEQ ID NO:1 and refers to nucleotides 1-499 of SEQ ID NO:1.

Regarding SEQ ID NOs:2 and 4, the sequence listing of the present application shows that the coding region of SEQ ID NO:2 is nucleotides 163 - 4098. The sequence listing of the present application also shows that the coding region of SEQ ID NO:4 is nucleotides 50 - 3454. Thus, it is clear in view of the disclosure that the recitation "coding portion" is not needed to

describe nucleotides 163-4098 of SEQ ID NO:2 or nucleotides 50-3454 of SEQ ID NO:4. Accordingly, it is Applicant's position that it is clear in view of the disclosure that the recitation "coding portion" is directed to SEQ ID NO:1, and not SEQ ID NO:2 or SEQ ID NO:4.

Claim 6 was rejected over the recitation "substantially." Claim 6 has been amended to recite "at least 90% homology." It is submitted that the metes and bounds of the claimed invention are clear.

It is respectfully submitted that the scope of claims 5 and 6 is clear to a person of ordinary skill. The Examiner is respectfully requested to reconsider and withdraw the §112, second paragraph, rejections.

Rejections under 35 U.S.C. §102(b)

Claims 1-3 were rejected under 35 U.S.C. §102(b) as being anticipated by Gispert et al. (*Nature Genet.*, 4, 295-299 (1993)). This rejection, as it relates to the pending claims, is respectfully traversed.

Claim 1 has been amended to recite an isolated mouse or human nucleic acid encoding an SCA2 polypeptide. Gispert et al. do not teach an isolated mouse or human nucleic acid encoding an SCA2 polypeptide. Gispert et al. teach the assignment of the human autosomal dominant cerebellar ataxia SCA2 to chromosome 12q23-24.1. As Gispert et al. do not teach an isolated mouse or human nucleic acid encoding an SCA2 polypeptide, Gispert et al. do not anticipate the claims of the present invention. Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

Claims 1-3 were rejected under 35 U.S.C. §102(b) as being anticipated by Pulst et al. (*Nature Genet.*, 1, 8-10 (1993)). This rejection, as it relates to the pending claims, is respectfully traversed.

Claim 1 has been amended to recite an isolated mouse or human nucleic acid encoding an SCA2 polypeptide. Pulst et al. do not teach an isolated mouse or human nucleic acid encoding an SCA2 polypeptide. Pulst et al. teach the identification of a human pedigree with linkage to 12q and establishment of flanking markers for SCA2. As Pulst et al. do not teach an

isolated mouse or human nucleic acid encoding an SCA2 polypeptide, Pulst et al. do not anticipate the claims of the present invention. Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

Claims 1-6 were rejected under 35 U.S.C. §102(b) as being anticipated by Imbert et al. (*Nature Genet.*, 14, 285-291 (1996)). This rejection, as it relates to the pending claims, is respectfully traversed.

It is Applicant's position that Imbert et al. is not prior art to the portion of the present application that was disclosed in U.S. Patent Application Serial No. 08/727,084 ('084), including, for instance, SEQ ID NO:1, SEQ ID NO:2, and SEQ ID NO:3. The present application is a national stage filing of PCT/US97/07725, which is a continuation in part of the '084 application, filed October 8, 1996. The first page of Imbert et al. indicates that it was published November, 1996, i.e., after the filing date of the '084 application. Since Imbert et al. is not prior art to the portion of the present application that was disclosed in the '084 application, reconsideration and withdrawal of the rejection as it relates to the portion of the present application that was disclosed in the '084 application is requested.

With respect to the portion of the present application that was not disclosed in the '084 application, including, for instance, portions of SEQ ID NO:4 and SEQ ID NO:5, it is respectfully submitted that Imbert et al. do not teach an isolated mouse nucleic acid encoding an SCA2 polypeptide. As Imbert et al. do not teach an isolated mouse nucleic acid encoding an SCA2 polypeptide, Imbert et al. do not anticipate the claims of the present invention. Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

Claims 1-6 were rejected under 35 U.S.C. §102(b) as being anticipated by Tora et al. (WO 97/17445). This rejection is respectfully traversed.

It is Applicant's position that Tora et al. is not prior art. In prosecuting a U.S. national stage application, "the international filing date is the date to keep in mind when searching the prior art . . . . " M.P.E.P. §1893.03. The present application is a national stage application under the PCT (filed under 35 U.S.C. §371) of PCT/US97/07725. The international filing date of PCT/US97/07725 is May 8, 1997. The international publication date of Tora et al. is May 15,

1997, which is after the international filing date of the present application. Since Tora et al. is not prior art, reconsideration and withdrawal of this rejection is respectfully requested.

Claim 4 was rejected under 35 U.S.C. §102(b) as being anticipated by Hillier et al. (Genbank Accession Number AA76524), and as being anticipated by Ambrose et al. (Genbank Accession Number L27350). Claim 4 has been canceled, thereby rendering these rejections moot.

Claims 5-6 were rejected under 35 U.S.C. §102(b) as being anticipated by Pulst et al. (*Nature Genet.*, 14, 269-276 (1996)). This rejection, as it relates to the pending claims, is respectfully traversed.

It is Applicant's position that Pulst et al. is not prior art to the portion of the present application that was disclosed in U.S. Patent Application Serial No. 08/727,084 ('084), including, for instance, SEQ ID NO:1, SEQ ID NO:2, and SEQ ID NO:3. The present application is a national stage filing of PCT/US97/07725, which is a continuation in part of the '084 application, filed October 8, 1996. The first page of Pulst et al. indicates that it was published November, 1996, i.e., after the filing date of the '084 application. Since Pulst et al. is not prior art to the portion of the present application that was disclosed in the '084 application, reconsideration and withdrawal of the rejection as it relates to the portion of the present application that was disclosed in the '084 application is requested.

With respect to the portion of the present application that was not disclosed in the '084 application, including, for instance, portions of SEQ ID NO:4 and SEQ ID NO:5, Applicant notes that Pulst et al. disclose Genbank Accession Number U70670, which teaches a mouse SCA2 cDNA sequence. It is Applicant's position that the disclosure of Genbank Accession Number U70670 is not prior art.

The present application is a national stage filing of PCT/US97/07725, which is a continuation in part of U.S. Patent Application Serial No. 08/727,084 ('084), filed October 8, 1996. SEQ ID NO:4 of the '084 application discloses a sequence of 1257 nucleotides, which is described as a partial mouse SCA2 cDNA at page 43, line 1, of the '084 application. SEQ ID NO:4 of the '084 application and the nucleotide sequence disclosed at Genbank Accession

Number U70670 are identical. The '084 application was filed October 8, 1996. The create date of Genbank Accession Number U70670 was November 20, 1996 (see page 4 of Exhibit A, an ASN.1 printout of Genbank Accession Number U70670), thus Genbank Accession Number U70670 was made publicly available after the '084 application was filed. Applicant is confirming that Genbank Accession Number U70670 was not publically available before October 8, 1996. Accordingly, the disclosure of Genbank Accession Number U70670 is not prior art. Since the disclosure by Pulst et al. of Genbank Accession Number U70670 is not prior art, reconsideration and withdrawal of this rejection is respectfully requested.

The Examiner is requested to note that at paragraphs 11, 12, and 15 of the Action the phrase "limitations of claim . . . 10" is used. At paragraph 15 of the Action the phrases "limitations of claim 11" and "limitations of claim 37" are used. Applicant does not understand to what these refer. Claims 10, 11, and 37 are not pending in the present application. The Examiner is respectfully requested to clarify to what the phrases "limitations of Claim . . . 10," "limitations of claim 11," and "limitations of Claim 37" refer.

Rejections under 35 U.S.C. §102(a)

Claims 6 and 59-61 were rejected under 35 U.S.C. §102(a) as being anticipated by Nechiporuk et al. (Genbank Accession Number AF041472). This rejection is respectfully traversed.

It is Applicant's position that Nechiporuk et al. is not prior art. In prosecuting a U.S. national stage application, "the international filing date is the date to keep in mind when searching the prior art . . . . " M.P.E.P. §1893.03. The present application is a national stage application under the PCT (filed under 35 U.S.C. §371) of PCT/US97/07725. The international filing date of PCT/US97/07725 is May 8, 1997.

SEQ ID NO:4 and SEQ ID NO:5 of the present application are disclosed in PCT/US97/07725 as SEQ ID NO:4 and SEQ ID NO:5, thus SEQ ID NO:4 and SEQ ID NO:5 have a priority date of May 8, 1997. According to the information available on the Internet at Genbank accession number AF041472 in the Genbank database, the sequence disclosed in

Nechiporuk et al. was submitted January 7, 1998. Thus, the sequence disclosed in Nechiporuk et al. could not have been publically available in the Genbank database before May 8, 1997, the international filing date of PCT/US97/07725. Accordingly, Nechiporuk et al. is not prior art.

The Examiner is respectfully requested to reconsider and withdraw the rejection of claims 6 and 59-61 under 35 U.S.C. §102(a) as being anticipated by Nechiporuk et al. (Genbank Accession Number AF041472).

Rejections under 35 U.S.C. §103

Claim 7 was rejected under 35 U.S.C. §103(a) as being unpatentable over Gispert et al. (*Nature Genet.*, 4, 294-299(1993)) in view of Orr et al. (U.S. Patent 5,741,645). This rejection is respectfully traversed.

Gispert et al. pertain to the chromosomal assignment of a second disease locus (SCA2) for dominantly inherited SCA to chromosome 12q23-24.1. The authors note that the autosomal dominant cerebellar ataxias are a clinically heterogenous group of disorders having inter-familial variation in several aspects of the disease that may reflect genetic heterogeneity or pleiotrophy. It is disclosed that positional cloning of the individual genetic mutations is likely to provide the only effective method form establishing a definitive classification system.

Gispert et al. disclose that a population was identified having a disease phenotype that is indistinguishable from that observed in pedigrees mapping to the SCA1 locus, but the disease phenotype was not linked to SCA1. Linkage analysis between the SCA2 locus and marker loci in two pedigrees was carried out. Genotype analysis was carried out following PCR amplification. It is not clear if chromosome 12 was actually isolated. Positioning of the disease locus in relation to the existing genetic linkage map indicated that SCA2 was located within the interval flanked by D12S58 and PLA2. However, the authors disclose that the comparatively large genetic distances between SCA2 and the closest linked loci, D12S58, IGF1, and PLA2, preclude their use in genetic counseling, and they further disclose that the immediate objective is the identification of a set of ordered and tightly linked markers which are pivotal to the positional cloning strategy and the provision of accurate presymptomatic and prenatal diagnosis.

Orr et al. pertain to an isolated DNA sequence of the short arm of chromosome 6 which is located within the autosomal dominant spinocerebellar ataxia type 1 gene. The authors disclose the linkage of the SCA1 locus to specific markers present on chromosome 6 and the process of cloning the SCA1 gene (col. 8 through col. 24). The isolated DNA sequence contains a polymorphic CAG repeat region. The number of trinucleotide repeats can vary from as few as 19, for example, to as many as 81, for example (col. 2, lines 5-8). It is disclosed that a gene probe is useable in a method of diagnosing a patient for SCA1 (col. 2, lines 50-51). A gene probe is a portion of a nucleotide sequence of the SCA1 gene having at least about 200 nucleotides (col. 2, lines 39-41). It is disclosed that the probe can contain any portion of the isolated DNA sequence, including any portion of the CAG region; however, it is desirable for the probe to contain a portion of the SCA1 gene on either side of the CAG region (col. 2, lines 44-49). Orr et al. also disclose oligonucleotides for diagnosing the neurodegenerative disorder SCA1 (col. 2, lines 64-66). The oligonucleotides include a nucleotide sequence capable of hybridizing to a portion of an SCA1 gene having a CAG repeat region (col. 2, line 66 through col. 3, line 2).

In the Action at the discussion of the Orr et al. document (page 12 of the Office Action, lines 8 and 12 of the first paragraph), the phrases "limitations of Claim 37" and "limitations of Claim 40" are used. Applicant does not understand to what these refer. Claims 37 and 40 are not pending in the present application, and the Orr et al. patent does not contain claims 37 or 40. The Examiner is respectfully requested to clarify to what the phrases "limitations of Claim 37" and "limitations of Claim 40" refer.

It is respectfully submitted that the Examiner has not met the burden of establishing a *prima facie* case of obviousness of the claimed invention. The requisite motivation to combine Gispert et al. with Orr et al. cannot be found in either Gispert et al. or Orr et al. It is axiomatic that motivation to combine documents cannot be attributed to the combination itself, and there is no showing of the existence in either cited document of a motivation to combine the disclosures to produce the claimed invention. Each document is examined in the following paragraphs for the existence of the requisite motivation.

Applicant submits that the skilled worker would not be motivated by reading Gispert et al. to combine the disclosure of Gispert et al. with the disclosure of Orr et al. to yield the present invention. Gispert et al. is directed to mapping the position of SCA2, and state that an immediate objective is the identification of ordered and tightly linked markers for use in positional cloning. However, Gispert et al. disclose that the disease locus present in the population used in the mapping analysis is not linked to SCA1. Thus, a person of ordinary skill would not be motivated to modify Gispert et al. to include the teachings of Orr et al.

Moreover, Gispert et al. do not teach or suggest that the nucleotide sequence of the SCA2 locus and the SCA1 locus are similar. In fact, Gispert et al. disclose that inter-familial variation in symptoms of the autosomal dominant cerebellar ataxias may reflect genetic heterogeneity or pleiotrophy (page 295, col. 1, second paragraph), and locus heterogeneity (page 295, col. 2, first full paragraph). Thus, Gispert et al. teach away from the use of the SCA1 gene as a probe for the SCA2 gene.

It is further submitted that the skilled person would not be motivated by reading Orr et al. to combine the disclosure of Orr et al. with the disclosure of Gispert et al. to yield the present invention. Orr et al. is directed to the mapping and cloning of the SCA1 gene. Orr et al. do not teach or suggest using the map position of SCA2 to map or clone the SCA1 gene. Moreover, Orr et al. do not teach or suggest that the nucleotide sequence of the SCA1 locus and the SCA2 locus are similar.

Applicant submits that even if the cited documents were combined, there would be no reasonable expectation of success that the methods used by Orr et al. would lead to the identification of the SCA2 locus. Gispert et al. suggest the positional cloning of the human SCA2 locus; however, this is at most an invitation for further experimentation, as Gispert et al. also state that more work is needed before a positional cloning strategy can be implemented (page 298, col. 1, first full paragraph). Moreover, combination of the cited documents would not result in all the claim limitations. Specifically, none of the cited documents teach or suggest a vector as recited in claim 7.

Even if a *prima facie* case of obviousness has been established, which the Applicant

argues is not the case, the Applicant strongly maintains that the claimed invention is not obvious in view of the cited combination of references. The methods of Orr et al. to use the nucleotide sequences of the SCA1 gene as a probe were never intended to be used to identify the SCA2 gene.

For the reasons set forth above, Applicant submits that the invention of claim 7 is nonobvious over the combination of Gispert et al. and Orr et al. Accordingly, Applicant respectfully requests reconsideration and withdrawal of the rejection of claim 7 in view of the cited documents.

Conclusion

Applicant respectfully submits that the claims are in condition for allowance and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicant's attorney (612-305-1005) to facilitate prosecution of this application.

If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 13-4895.

Respectfully submitted,
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February 20, 2001
Date
DLP/mi

By: David L. Provence
David L. Provence
Reg. No. 43,022
Direct Dial (612) 305-1005

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Date of Deposit: February 20, 2001
Express Mail label number: EL776901777US

David L. Provence
Name: David L. Provence

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FEB 20 2001
PATENT & TRADEMARK OFFICE

Applicant(s): Stefan M. Pulst
Serial No. 08,981,998
Filed 11 May 1998
NUCLEIC ACID ENCODING SPINOCEREBELLAR ATAXIA-2 AND PRODUCTS RELATED THERETO
Attorney Docket No. 256.00010120

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APPENDIX A
PENDING CLAIMS WITH MARK-UPS

1. Isolated mouse or human nucleic acid encoding [a mammalian] an SCA2 polypeptide.

2. Isolated nucleic acid according to claim 1, wherein said nucleic acid comprises DNA.

3. DNA according to claim 2, wherein said DNA is cDNA.

4. (Canceled)

5. DNA according to claim 2, wherein said DNA hybridizes under high stringency conditions to the SCA2 coding portion of nucleotides 1 - 516 of SEQ ID NO:1 or nucleotides 163-4098 of SEQ ID NO:2, or nucleotides 50-3454 of SEQ ID NO:4.

6. (Amended) DNA according to claim 2, wherein said DNA has at least 90% homology to [substantially the same nucleotide sequence as] the SCA2 coding portion set forth in SEQ ID NO:2, or the SCA2 coding portion set forth in SEQ ID NO:4.

7. A vector comprising DNA according to claim 2.

59. An isolated nucleic acid encoding the amino acid sequence set forth at SEQ ID NO:5.

60. (Canceled)

61. (Amended) The isolated nucleic acid of claim 1 [60], wherein the nucleotide sequence is set forth at SEQ ID NO:4.

62. (New) An isolated nucleic acid, wherein the nucleic acid hybridizes under high stringency conditions to nucleotides 1 - 516 of SEQ ID NO:1, nucleotides 163-4098 of SEQ ID NO:2, or nucleotides 50-3454 of SEQ ID NO:4, wherein the isolated nucleic acid encodes an SCA2 polypeptide.

63. (New) An isolated nucleic acid, wherein the nucleic acid hybridizes under high stringency conditions to nucleotides 50-3454 of SEQ ID NO:4, wherein the isolated nucleic acid encodes an SCA2 polypeptide.

64. (New) An isolated nucleic acid, wherein the nucleic acid hybridizes under high stringency conditions to nucleotides 1 - 516 of SEQ ID NO:1, or nucleotides 163-4098 of SEQ ID NO:2, wherein the isolated nucleic acid encodes an SCA2 polypeptide.

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☐ 1: U70670 **Mus musculus ataxin-2 mRNA, partial cds**

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Exhibit A

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DVSNGWDPNDMFRYNEENYGVVSTYDSSLSSYTVPLERDNSEEFLKREARANQLAEEIESSAQYKARVALENDDRSEE
EKYTAVQRNCSDREGHGPNTRDNKYIPPGQRNREVLSWGSGRQSSPRMGQPGPGSMPSRAASHTSDFNPNAGSDQRVV
NGGVPWPSPCPSPSSRPPSRYQSGPNSLPPRAATPTRPRAEFLQPGDP" } ,
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        {
          data
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              {
                data
                  prot {
                    name {
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                partial TRUE ,
                location
                  whole
```

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                  to 1256 ,
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                  fuzz-from
                    lim lt ,
                  fuzz-to
                    lim gt } } } } } }
```

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